Mitigation of pain and anaesthetic drugs

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Abstract
Introduction
Anaesthetics are used for pain management in patient surgery. They may interact with different levels of pain transmission in the body and by doing so anaesthetics encounter with the immune system. Due to this, alterations in immune response occurs which may lead to complications in patients after surgery. This review discusses the mitigation of pain and anaesthetic drugs.

Discussion
Literature search revealed that there are four elements of pain transmission viz. transduction, transmission, modulation and perception. The nociceptive pathway is involved in the experience of pain and is modified by both psychosocial factors and damage/ or inflammation within tissues. There are different types of anaesthetics used by the clinicians which have an effect on one or more elements of pain transmission. Use of anaesthetics during preoperative treatment has an impact on immune elements which results in other ailments in patients post operatively.

Conclusion
Anaesthetics manage pain using various mechanisms. There is a need to explore and use multi modal techniques of anaesthetics that have minimum post operative side effects.

Introduction
The international association for the study of pain (IASP) defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” or described in terms of such damage. Several broad processes associated with pain viz., nociception, pain perception and a number of secondary consequences such as suffering as well as pain behavior may be useful in clinical settings. Nociception is the process which involves the detection of noxious stimuli and subsequent transmission of encoded information to the brain. On the other hand pain is a perceptual process that arises in response to such activity (Figure 1).

Primary afferent neurons in cutaneous and deep somatic tissues synapse with second order neurons in the dorsal horn of the spinal cord. They have three functions with respect to their role in nociception:

1. Detection of noxious or damaging stimuli.
2. Passage of the resulting sensory input from peripheral terminals to the spinal cord.
3. Synaptic transfer of this input to neurons within specific laminae of the dorsal horn.

Information from the noxious stimuli in the form of sensory information is then relayed to supraspinal structures including the thalamus and brainstem. In descending modulatory systems powerful internal controls are present at all levels which exemplify the signal.

Nociceptors are unspecialized, free, unmyelinated nerve endings that convert (transduce) a variety of stimuli into nerve impulses to produce the sensation of pain. The nerve cell bodies are located in the dorsal root ganglia or for the trigeminal nerve in the trigeminal ganglion, and they send one nerve fibre branch to the periphery and another into the spinal cord or brainstem. The nociceptors are distributed in the somatic and visceral structures. They are exposed to noxious stimuli when tissue damage and inflammation occurs. The nerve fibre of the nociceptor is of two types i.e., C fibres and A delta fibres. C fibres have a small diameter, unmyelinated nerves and conduct nerve impulse slowly (2m/sec) while A-delta fibres have a large diameter, lightly myelinated nerves and conduct nerve impulse faster (20m/sec). The C fibre and A-delta fibres are associated with different qualities of pain viz. diffuse/well-localised, dull/sharp, burning/stinging, and aching/pricking respectively (Figure 1).

Nowadays, in the fields of immunology and anaesthesia rapid developments have taken place. It has been proposed by anaesthesiologists that anaesthesia dysregulate or suppress the immune system during the perioperative period which may provoke postoperative complications, e.g., wound-healing disturbances and infections leading to sepsis, followed by multiple organ failure and death. The immunological effects of surgery and anaesthetics affect the long-term outcomes of patients after surgery. Therefore, awareness of these immunological properties is helpful for daily anaesthetic management. The aim of this review was to discuss mitigation of pain and anaesthetic drugs.

Discussion
Pain and its processing
Acute pain has been defined as the normal, predicted, physiological response to an adverse chemical, thermal, or mechanical stimulus. Acute pain-induced change in the central nervous system is known as neuronal plasticity. In the nervous system neuroplastic changes occur due to tissue injury, which results in peripheral and central sensitization. The four elements of pain processing include transduction, transmission, modulation, and perception.

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Transduction of pain
In brief, transduction of pain is the event whereby noxious chemical, thermal, or mechanical stimuli are converted into an action potential. It begins when the free nerve endings (nociceptors) of C fibres and A-delta fibres of primary afferent neurons respond to noxious stimuli. Externally or internally stimulated noxious stimuli (mechanical, thermal or chemical) causes a release of chemical mediators from the damaged cells such as prostaglandin, bradykinin, serotonin, substance P, potassium, and histamine.

These chemical mediators activate and/or sensitize the nociceptors to the noxious stimuli. In order for a pain impulse to be generated, an exchange of sodium and potassium ions (depolarization and repolarization) occurs in nerve cell membranes. This results in an action potential and generation of a pain impulse.

Transmission of pain
It occurs when the action potential is conducted through the nervous system via the first, second, and third-order neurons, which have cell bodies located in the dorsal root ganglion, dorsal horn, and thalamus, respectively. The transmission of pain impulses occur in three stages:
- From the site of transduction along the nociceptor fibres to the dorsal horn in the spinal cord
- From the spinal cord to the brain stem
- From brain stem to the thalamus, cortex and higher levels of the brain.

The C fibre and A-delta fibres terminate in the dorsal horn of the spinal cord. There is a synaptic cleft between the terminal ends of these fibres and the nociceptive dorsal horn neurones (NDHN).

Excitatory neurotransmitters (adenosine triphosphate, glutamate, calcitonin gene-related peptide, bradykinin, nitrous oxide, and substance P) are released in order to transmit the pain impulse across the synaptic cleft to the NDHN, excitatory neurotransmitters bind to specific receptors in the NDHN. The pain impulse is then transmitted from the spinal cord to the brain stem and thalamus mainly via spinothalamic and spinoparabrachial nociceptive ascending pathways. When impulses arrive in the thalamus they are directed to multiple areas in the brain for processing.

Modulation of pain
Modulation of pain transmission involves altering afferent neural transmission along the pain pathway. The dorsal horn of the spinal cord is the most common site for modulation of
the pain pathway, and modulation can involve either inhibition or augmentation of the pain signals\(^7\). The multiple, complex pathways involved in the modulation of pain are referred to as the descending modulatory pain pathways (DMPP).

Descending inhibition involves the release of inhibitory neurotransmitters (e.g., endogenous opioids, serotonin, norepinephrine, gamma-aminobutyric acid, neuropeptides, acetylcholine, and oxytocin) that block or partially block the transmission of pain impulses, and therefore produce analgesia\(^7\).

**Perception of pain**
Perception of pain is the final common pathway, which results from the integration of painful input into the somatosensory and limbic cortices. Generally speaking, traditional analgesic therapies have only targeted pain perception. A multimodal approach to pain therapy should target all four elements of the pain processing pathway.

The multidimensional experience of pain has affective-motivational, sensory-discriminative, emotional and behavioural components. When the painful stimuli are transmitted to the brain stem and thalamus, multiple cortical areas are activated and responses are elicited. These areas are the reticular, somatosensory cortex and limbic systems. The reticular system is responsible for the autonomic and motor response to pain and for warning the individual to do something. The somatosensory cortex is involved with the perception and interpretation of sensations. The limbic system is responsible for the emotional and behavioural responses to pain.

**Anaesthetics and their mode of action**
Anaesthesia is a controlled, reversible intoxication of the nervous system and anaesthetics are the moieties which eliminates patient's pain by altering physiology of the patient. The main types of anaesthesia are local, regional, and general. Regional anaesthesia numbs a larger area of the body than local anaesthesia and may be used for many operations below the waist. Major types of regional anaesthesia are spinal, epidural and peripheral nerve block. General anaesthesia relaxes the muscles, puts in sleep, and keeps patients from feeling pain. The anaesthetic may be given through a vein (IV), or as a gas breathed in through a mask. Local anaesthesia numbs the part of the body where surgery has to be done.

Local anaesthetics are a group of drugs with the ability to prevent sodium entry into axons, thereby preventing the generation of propagated action potentials in axons.

They also have other actions, however, such as prevention of axonal sprouting and effects on G-protein-coupled receptors, and on conductance of ions in addition to sodium that might be important in the management of pain. Local anaesthetics are used in a wide range of clinical situations to prevent acute pain and to stop or ameliorate pain produced by cancer or pain associated with chronic painful conditions\(^8\). They may act to produce a desired anaesthetic or analgesic effect at any part of the nervous system i.e. from the periphery to the brain (Figure 2).

**Bupivacaine**
It is an amide type local anaesthetic mainly used for surgical, obstetric, acute and chronic pain therapy. Most local anaesthetics, including the amide type anaesthetics, are described as state dependent Na\(^+\) channel pore blockers. Nilsson et al.\(^9\) suggests that anaesthetic action of bupivacaine in myelinated axons is primarily due to inhibition of the Na\(^+\) channels. Important clinical properties of bupivacaine are a relatively high potency and a capacity to block sensory and motor fibres differently. It has been widely used extradurally for both obstetric and surgical procedures and post operative pain relief. Bupivacaine is more potent than other local anaesthetics such as lidocaine, procaine and benzocaine\(^9\).

**Ketamine**
Ketamine produces dose-related unconsciousness and analgesia. The ketamine-anaesthetized patients have profound analgesia but keep their eyes open and maintain many reflexes. It selectively depresses neuronal function in the cortex and thalamus while simultaneously stimulates parts of the limbic system. It is reported that

**Figure 3:** Elements of pain and their blockage by different agents.
ketamine occupies opiate receptors in the brain and spinal cord, which could account for its analgesic effects. Analgesic effect in the spinal cord may be due to inhibition of the dorsal horn vide dynamic range neuronal activity⁶.

**Paracetamol**

It is also known as acetaminophen and remains the most popular analgesic. Despite its popularity the mechanism by which paracetamol achieves its effects on pain is still debated. It has been assumed that paracetamol probably acts through the cyclooxygenase (COX) pathway. Alternative proposed mechanisms include reinforcement of descending inhibitory serotonergic pain pathways, inhibition of the L-arginine-nitric oxide (NO) pathway mediated through substance P, and active paracetamol metabolites that have an effect on cannabinoid (CB) receptors⁶¹⁰.

One of the active metabolites of paracetamol (the fatty acid amide N-arachidonoylphenolamine) shares the ability of the cannabinoid receptor to display analgesic activity and to lower body temperature¹¹ (Figure 3).

**Dextromethorphan**

It is the dextrorotatory enantiomer of the fatty acid amide N-arachidonoylphenolamine. It is quickly absorbed in the gastrointestinal tract after oral administration, after that via the bloodstream it crosses the blood-brain barrier and reaches the cerebral spinal fluid¹².

As a noncompetitive N-methyl-D-aspartate (NMDA) antagonist, dextromethorphan decreases glutamate activity. This attribute suggests a potential neuroprotective role for conditions such as amyotrophic lateral sclerosis, methotrexate neurotoxicity or a reduction of pain sensation by reducing the excitatory transmission of the primary afferent pathways along the spinothalamic tract⁶.

### Anaesthesiology and Immune Response

Rapid development has taken place during recent decades, in the fields of anaesthesia and immunology.

It is a well established fact among anaesthesiologists that dysregulation/suppression of the immune system during the perioperative period provokes postoperative complications which includes wound-healing disturbances and infections leading to sepsis, followed by multiple organ failure and death³. In cancer patients after surgery, the development of residual cancer cells and the establishment of new metastases are accelerated by immunosuppression.

The immunological effects of anaesthesia and surgery affect the long-term outcomes of patients after surgery. Awareness of these immunological properties may be helpful for pain management¹³.

Surgical stress induces release of hormones such as adrenocorticotrophic hormone (ACTH), catecholamines, and cortisol, via the autonomic nervous system. The hypothalamic pituitary adrenal axis mediates inhibitory effects on immune functions, because monocytes, macrophages and T cells have both β2-adrenoreceptors and glucocorticoid receptors, which promote cellular signalling to inhibit the production of representative Th1 (helper-T-cell 1) cytokines such as interleukin-12 (IL-12) and interferon-γ (IFN-γ), and to produce Th2 cytokines, the so-called antiinflammatory cytokines, such as IL-4 and IL-10³.

Although these Th2 cytokines act intrinsically to limit the exaggerated inflammatory responses induced by surgical trauma, the excessive or uncontrolled secretion of Th2 cytokines engenders immunosuppression. Proinflammatory cytokines such as IL-1, IL-6, and tumour necrosis factor (TNF-α) from monocytes and macrophages and lymphocytes activated by surgical stress can stimulate the hypothalamic-pituitary-adrenal (HPA) axis⁵. Therefore, the neuroendocrine system, and proinflammatory cytokines and anti-inflammatory cytokines, synergistically augment their suppressive effects in the perioperative immune system.

Indeed, this immunosuppressive network manifested by the activated neuroendocrine system and hypercytokinemia during the perioperative period may adversely affect long-term clinical outcomes.

Many studies have revealed the concentration and time dependent immunosuppressive effects of anaesthetics on various immune cells such as neutrophil, natural killer cell, monocyte, macrophage, and lymphocyte. Several studies confirmed that anaesthetics (halothane, enflurane, isoflurane, and sevoflurane) inhibit reactive oxygen species production by activated neutrophils. It is believed that the mechanism behind this process involves either a direct NADPH oxidase inhibitor or an inhibitory effect at some site in its regulatory signal transduction pathway, such as protein kinase C inhibition¹⁴. NK cells can kill certain tumour cells and virus-infected cells naturally without prior sensitization or MHC restriction. These cells function as surveillance in the early tumour developmental stage and killing tumour cells. By producing IFN-γ they also help in the priming process of antigen processing cells, tumour-specific Tc cells, and Th1 cells¹⁵. Due to blood transfusion or the activation of the neuroendocrine system, anti-inflammatory cytokines are produced by immune cells. These cytokines (IL-4 and IL-10 i.e., Th2 cytokines) are known to suppress NK cell mediated tumour immunity. It has been found that anaesthetics (halothane and enflurane) can reversibly inhibit NK cell activity in a concentration dependent manner. An in vivo study indicated that the tumour metastases increase by the halothane induced suppression of NK cell activity³,¹⁶.

Inhibitory effects of anaesthetics on lymphocyte proliferation and cytokine

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**Conflict of interests:** None declared.

**All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.**

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Competing interests: None declared. Conflict of interests: None declared. Attribution

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Review
release in peripheral blood mononuclear cells have been shown in various studies. These effects on lymphocytes may reduce their immunocompetence against microorganisms and tumour cells.

The mechanisms by which anaesthetics inhibit lymphocyte function remain unclear. It is believed that the release of cytochrome C from the mitochondria, decrease of mitochondrial membrane potential, and interference with the MAPK cascade are the possible mechanisms for anaesthetic induced inhibitory or anti-inflammatory effects on lymphocytes.

**Conclusion**

Changes in the sensitivity of nociceptive neurons under the development of the tissue hypersensitivity associated with inflammation. Recent advances in molecular neuroscience continue to provide tremendous opportunities for understanding the molecular actions of general anaesthetics on their targets. There is a need to develop anaesthetics that have multiple targets and lower side effects on the immune system after surgery. This may help in the management of pain as well as to get better outcomes of anaesthetics.

**References**